TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
09672		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/014684	29.09.2004	30.09.2003

International Patent Classification (IPC) or national classification and IPC

C07D257/04, A61K31/41, 31/437, 31/4709, 31/5377, 31/541, A61P3/10, 13/12, C07D401/10,413/10, 417/10, 471/04

Applicant

SANKYO COMPANY, LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/014684

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/014684

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 20,21

because:

☒ the said international application, or the said claims Nos. 20,21 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claims 20 and 21 relates to methods for treatment of the human body by therapy. Thus, this International Preliminary Examining Authority is not required to carry out international preliminary examination on this subject matter under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 20,21

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/014684

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 7-11, 13-19, 22-25	YES
	Claims	1-4, 6, 12	NO
Inventive step (IS)	Claims	5, 7	YES
	Claims	1-4, 6, 8-19, 22-25	NO
Industrial applicability (IA)	Claims	1-19, 22-25	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Kim, Moohi Yoo et al., "Synthesis, biological properties and structure-activity relationships of 2-oxoquinoline derivatives, new nonpeptide angiotensin II reception antagonists", Korean Journal of Medicinal Chemistry, 1995, Vol. 5, No. 1, pages 28 to 37

Document 2: Michio Ueno, "ARB no Jin Hogo to Ketsuatsu no Kanren", Japanese Journal of Clinical Medicine, 1 October 2002, Vol. 60, No. 10, pages 1999 to 2004

Document 3: WO 2002/083127 A1 (Toshio Miyata), 24 October 2002

Document 4: JP 2002-255813 A (Fuso Chemical Co., Ltd.), 11 September 2002

Claims 1 to 4, 6 and 12

The invention set forth in claims 1 to 4, 6 and 12 is disclosed in document 1 cited in the international search report, and therefore lacks novelty and does not involve an inventive step.

Document 1 sets forth 2-oxotetrahydroquinoline derivatives (compounds 44 and 45), and goes on to

indicate that said compounds have an angiotensin II receptor antagonist activity, and are useful in the treatment of hypertension.

Moreover, compounds 44 and 45 correspond to compounds where in the general formula (1), A is (A1), B is a 1H-tetrazole-5-yl group, X is methylene, Y is a C6-arylene (phenylene) group, R^{1A} is a C3 or C5 alkyl group, R^{2A} is hydrogen, and R^{3A} is an ethyl group.

Claims 14 to 16, 18, 19, 22 and 24 to 25

The invention set forth in claims 14 to 16, 18, 19, 22 and 24 to 25 does not involve an inventive step in the light of documents 1 and 2 cited in the international search report.

Document 2 indicates that angiotensin II plays an important role in the progress of renal damage localized in the kidneys, and, as a consequence, that angiotensin II receptor antagonists may be expected to suppress the progress of renal damage in addition to lowering the entire body's blood pressure. Document 2 also indicates that in large-scale clinical intervention trials of type-2 diabetic nephropathy, angiotensin II receptor antagonists losartan and irbesartan both exhibited kidney protection activity independently of changes in blood pressure.

Therefore, it would be easy for a person skilled in the art to conceive of confirming for angiotensin II receptor antagonists the AGEs production suppressing activity which is known to be closely related to the kidney protection effect, and to use the angiotensin II receptor antagonist in a pharmaceutical composition for the treatment and/or prevention of diabetic nephropathy

to constitute the inventions set forth in claims 14 to 16, 18, 19, 22, 24 and 25.

Claims 1 to 4, 8 to 19 and 22 to 25

The invention set forth in claims 1 to 4, 8 to 19 and 22 to 25 does not involve an inventive step in the light of document 3 cited in the international search report.

Document 3 sets forth a composition which suppresses the production of protein modulators such as advanced glycation end-products (AGEs). In addition, document 3 indicates that a compound with a biphenyl tetrazole group such as valsartan exhibits a protein modulator suppressing effect, and can be used as the active ingredient of the aforementioned composition; and that the composition which suppresses the generation of protein modulators is particularly useful in the prevention and/or treatment of renal damage and diabetes complications (nephropathy, etc.).

Comparing the invention set forth in claims 1 to 4, 8, 9, 12 to 19 and 22 to 25 of this application with the invention set forth in document 3, the two only differ in that in the invention set forth in claims 1 to 4, 8, 9, 12 to 19 and 22 to 25 of this application, the substituent on the nitrogen atom in general formula (IA3) is a phenyl group having carboxylic acid, while in the valsartan set forth in document 3, the substituent on the nitrogen atom is an isobutyl group having carboxylic acid.

This difference is examined below.

It is common practice to immobilize the partial structure necessary for expression of activity, and to produce a compound having another part of the structure

which has been changed, and to confirm the activity of said compound.

It would therefore be easy for a person skilled in the art to conceive of immobilizing the biphenyl tetrazole group of valsartan, and producing a compound with an isobutyl group having carboxylic acid on the nitrogen atom by a phenyl group having carboxylic acid, and confirming the AGEs production suppressing activity thereof, to constitute the invention set forth in claims 1 to 4, 8, 9, 12 to 19 and 22 to 25 of this application.

In addition, it is common practice to change the number of carbon atoms of the alkyl group in the alkyl carbonyl group, therefore it would be easy for a person skilled in the art to conceive of producing a compound having an alkyl group with a different number of carbon atoms in the alkyl carbonyl group, and confirming the AGEs production suppressing activity to constitute the invention set forth in claims 10 and 11 of this application.

Claims 5 and 7

The invention set forth in claims 5 and 7 is not disclosed in any of the documents cited in the international search report, and would not be obvious to a person skilled in the art.

Documents 1 to 4 do not set forth a compound represented by general formula (1), wherein B is a 2,4-dioxothiozolidine-5-yl group, and this feature offers the invention of this application the advantageous effect of a good AGEs production suppressing effect and being useful in the treatment of diabetes complications.